# Texas Medicaid/CHIP Vendor Drug Program
## Drug Utilization Criteria For Outpatient Use Guidelines
### Platelet Aggregation Inhibitors

**About**
Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

**Publication History**
Developed December 2016.

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**1. Dosage [*]**
*Adults*
Platelet aggregation inhibitors (PAIs) are FDA-approved to reduce thrombotic cardiovascular events in patients with a history of ischemic stroke, or to prevent stroke in patients with predisposing factors for atherosclerosis or symptomatic cerebrovascular disease.[1-11] PAIs work by interfering with pathways that promote normal platelet function: inhibiting cyclooxygenase-1 (e.g., aspirin); inhibiting adenosine uptake into platelets, resulting in increased cyclic-3',5'-adenosine monophosphate (cAMP) and adenosine levels (e.g., dipyridamole); inhibiting the adenosine diphosphate (ADP) $P2Y_{12}$ receptor on the platelet surface and blocking activation of the glycoprotein GPIIb/IIIa complex (e.g., clopidogrel, prasugrel, ticagrelor); antagonizing protease-activated receptor 1 (PAR-1), which inhibits thrombin and thrombin receptor agonist peptide activity (e.g., vorapaxar); or inhibiting phosphodiesterase lll (e.g., cilostazol).[2-4, 12]

Aspirin is available in combination with omeprazole, a proton pump inhibitor, to reduce the risk of aspirin-associated gastric ulcers in those patients requiring aspirin for secondary prevention of cardiovascular and cerebrovascular events.[2-4, 10] Aspirin is also available as combination therapy with dipyridamole, pairing two antiplatelet agents with different mechanisms of action for secondary stroke prevention.[2-4, 11]
Maximum recommended adult dosages for PAIs are summarized in Table 1. Medication profiles identifying patients prescribed dosages exceeding these recommendations will be reviewed.

| **Table 1: Maximum Daily Adult Dosages for PAIs[1-3, 5-11]** | | |
|---|---|---|
| **Drug** | **Dosage Form/Strength** | **Maximum Recommended Daily Dose** |
| *Monotherapy* | | |
| aspirin (Durlaza®) | 162.5 mg extended-release capsule | *reduce risk of death and recurrent stroke or recurrent MI in patients with a history of ischemic stroke or TIA, and/or a history of chronic coronary artery disease:* 162.5 mg once daily |
| cilostazol (generics) | 50 mg, 100 mg tablets | *intermittent claudication:* 100 mg twice daily |
| clopidogrel (Plavix®, generics | 75 mg, 300 mg tablets | *acute coronary syndrome (NSTE-ACS and STEMI):* following a 300 mg loading dose, 75 mg/day in combination with aspirin<br><br>*thromboembolism prophylaxis in patients with recent MI or stroke, or established peripheral vascular disease:* 75 mg/day |
| dipyridamole (generics) | 25 mg, 50 mg, 75 mg tablets | *prevention of postoperative thrombotic complications in patients with prosthetic heart valves:* 400 mg/day (divided doses, in combination with warfarin) or 300 mg/day (divided doses, in combination with aspirin) |
| prasugrel (Effient®) | 5 mg, 10 mg tablets | *acute coronary syndrome in patients to be managed with PCI:* following a 60 mg loading dose, 10 mg/day+ in combination with aspirin |
| ticagrelor (Brilinta®) | 60 mg, 90 mg tablets | *acute coronary syndrome:* following a 180 mg loading dose, 90 mg twice daily^ in combination with aspirin or clopidogrel |
| vorapaxar (Zontivity®) | 2.08 mg tablet | *MI, stroke, thrombosis prophylaxis in patients with a history of MI or peripheral arterial disease:* 2.08 mg/day in combination with aspirin or clopidogrel |
| *Combination Therapy* | | |
| aspirin/omeprazole (Yosprala®) | 81 mg/40 mg, 325 mg/40 mg delayed-release tablets | *secondary prevention of cardiovascular and cerebrovascular events in patients predisposed to gastric ulcers:* 325 mg/40 mg once daily |
| dipyridamole/aspirin (Aggrenox®, generics) | 200 mg/25 mg extended-release capsule | *stroke prevention:* 200 mg/25 mg twice daily |

*MI = myocardial infarction; TIA = transient ischemic attack; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; STEMI = ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention*
*+patients < 60 kg may use prasugrel 5 mg/day as maintenance therapy in combination with aspirin to reduce bleeding risk*
*^ticagrelor dosages are decreased to 60 mg twice daily after 12 months*

*Pediatrics*
Dipyridamole is FDA-approved for use in pediatric patients 12 years of age and older as adjunctive therapy to prevent thromboembolism following cardiac valve replacement. The maximum recommended dose is 100 mg four times daily in combination with warfarin. Dosages exceeding these recommendations will be reviewed.

Aspirin as Durlaza®, cilostazol, prasugrel, ticagrelor, vorapaxar, aspirin/omeprazole, and dipyridamole/aspirin are not recommended for use in pediatric patients as safety and efficacy have not been established for these agents in this patient population. Although not FDA-approved, clopidogrel has effectively been used in pediatric patients to reduce thrombosis risk in infants and children with select types of heart disease, or as an alternative in patients with Kawasaki disease or ischemic stroke when aspirin is not tolerated.[2, 3, 13-16]

## 2. Duration of Therapy

There is no basis for limiting PAI therapy duration when prescribed to prevent thromboembolic events associated with cardiovascular or cerebrovascular disease. However, PAI therapy duration varies, based on medication utilized and indication for use. PAI treatment durations are summarized in Table 2.

**Table 2: Maximum Treatment Duration for PAIs in Adults[1-3, 5-11, 17, 18]**

| Drug | Indication | Maximum Treatment Duration |
|---|---|---|
| *Monotherapy* | | |
| aspirin (Durlaza®) | *reduce risk of death and recurrent stroke or recurrent MI in patients with a history of ischemic stroke or TIA, and/or a history of chronic coronary artery disease* | indefinite |
| cilostazol (generics) | *intermittent claudication* | indefinite |
| clopidogrel (Plavix®, generics | *acute coronary syndrome (NSTE-ACS and STEMI)*<br><br>*thromboembolism prophylaxis* | up to 1 year, in combination with aspirin; aspirin then continued indefinitely[+]<br><br>indefinite |
| dipyridamole (generics) | *prevention of postoperative thrombotic complications in patients with prosthetic heart valves* | indefinite, in combination with warfarin or aspirin |
| prasugrel (Effient®) | *acute coronary syndrome in patients to be managed with PCI* | at least 12 months, in combination with aspirin, after stent placement |
| ticagrelor (Brilinta®) | *acute coronary syndrome* | 90 mg twice daily x 1 year in combination with aspirin; then, 60 mg twice daily in combination with aspirin indefinitely |
| vorapaxar (Zontivity®) | *MI, stroke, thrombosis prophylaxis in patients with a history of MI or peripheral arterial disease* | indefinite, in combination with aspirin or clopidogrel |
| *Combination Therapy* | | |
| aspirin/omeprazole (Yosprala®) | *secondary prevention of cardiovascular and cerebrovascular events in patients predisposed to gastric ulcers* | indefinite |
| dipyridamole/aspirin (Aggrenox®, generics) | *stroke prevention* | indefinite |

*MI = myocardial infarction; TIA = transient ischemic attack; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; STEMI = ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention*
*[+]in patients with aspirin allergy, clopidogrel monotherapy may be continued indefinitely*

### 3. Duplicative Therapy [*]

Combined administration of multiple PAIs may result in augmented antiplatelet effects. Adjunctive therapy with aspirin and clopidogrel, dipyridamole, prasugrel, ticagrelor, or vorapaxar has documented efficacy for acute coronary syndrome or thrombotic event prevention; concurrent therapy with clopidogrel and ticagrelor or vorapaxar is also FDA-approved for thromboembolic event prophylaxis or acute coronary syndrome (see Tables 1 and 2). Patients receiving concurrent therapy, however, should be observed for enhanced adverse effects due to similar mechanisms of actions between PAIs.[1-11, 17, 18]

### 4. Drug-Drug Interactions [*]

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Major drug-drug interactions considered clinically significant for platelet aggregation inhibitors are summarized in Table 3. Only those drug-drug interactions classified as clinical significance level 1/contraindicated or those considered life-threatening which have not yet been classified will be reviewed.

**Table 3: Major PAI Drug-Drug Interactions[1-3, 5-11, 19-21]**

| Target Drug | Interacting Drug | Interaction | Recommendation | Clinical Significance* |
|---|---|---|---|---|
| PAIs, including aspirin | low molecular weight heparins | potential for additive bleeding adverse effects; PAIs inhibit platelet aggregation and have increased bleeding risk, prolonged bleeding time | avoid concurrent therapy, if possible; if drug combination necessary, use cautiously, monitor for signs/symptoms of bleeding | major, moderate (DrugReax) 2-major, 3-moderate (CP) |
| PAIs, including aspirin | selective serotonin reuptake inhibitors (SSRIs)/ serotonin norepinephrine reuptake inhibitors (SNRIs) | increased bleeding risk with combined therapy; SSRIs/SNRIs deplete platelet serotonin, which may impair platelet aggregation | monitor for signs/symptoms of bleeding; may consider substituting tricyclic antidepressant for SSRI/SNRI | SSRIs –major; SNRIs-major (DrugReax) 3-moderate (CP) |
| PAIs, including aspirin | warfarin | combined administration may increase bleeding risk, due to additive effects | if combined therapy necessary, monitor patients closely for bleeding signs/symptoms | major (DrugReax) 2-major, 3-moderate (CP) |
| aspirin | methotrexate (MTX) | potential for increased MTX serum levels, risk of enhanced pharmacologic/toxic effects as NSAIDs can reduce MTX clearance | avoid concurrent NSAIDs within 10 days of high-dose MTX; otherwise, use cautiously together; monitor for increased myelopsuppressive, GI adverse effects; may consider using longer leucovorin rescue | major (DrugReax) 1-severe (CP) |

| **Table 3: Major PAI Drug-Drug Interactions (continued)**[1-3, 5-11, 19-21] | | | | |
|---|---|---|---|---|
| **Target Drug** | **Interacting Drug** | **Interaction** | **Recommendation** | **Clinical Significance*** |
| clopidogrel | dasabuvir/ ombitasvir/ paritaprevir/ ritonavir (Viekira®) | adjunctive administration with clopidogrel (strong CYP2C8 inhibitor) contraindicated by manufacturer, as dasabuvir is metabolized by CYP2C8, which increases risk for dasabuvir-induced QT interval prolongation; ritonavir, a CYP3A4 inhibitor, may limit clopidogrel conversion to active metabolite | avoid concurrent use | 1-severe (CP) |
| cilostazol, dipyridamole | riociguat (Adempas®) | concurrent administration may result in increased hypotension risk | avoid concurrent use | contraindicated (DrugReax) dipyridamole: 1-severe; cilostazol: 3-moderate (CP) |
| cilostazol, ticagrelor, vorapaxar | itraconazole, strong CYP3A4 inhibitors | co-administration may result in elevated serum concentrations of select PAIs and potential bleeding complications as cilostazol, ticagrelor, and vorapaxar metabolized by CYP3A4 | avoid use; ticagrelor therapy should not be initiated for at least 2 weeks after itraconazole discontinuation; if adjunctive administration necessary, use cautiously and monitor patient closely for enhanced pharmacologic/adverse effects, especially bleeding | ticagrelor: contraindicated; cilostazol, vorapaxar: major (DrugReax) ticagrelor: 1-severe; cilostazol, vorapaxar: 2-major (CP) |

**CP = Clinical Pharmacology; PAI – platelet aggregation inhibitor*

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